THE COUNCIL FOR TOBACCO RESEARCH—U.S.A., INC.
110 EAST 59TH STREET
NEW YORK, N.Y. 10022
(212) 421-8885

Application For Renewal of Research Grant

(Use extra pages as needed)

First Renewal ☐ Second Renewal ☒ Date: July 19, 1973

1. Principal Investigator (give title and degrees): Appendix I.

A. Clifford Barger, M.D.
Robert Henry Pfeiffer Professor of Physiology

J. Alan Herd, M.D.
Associate Professor of Physiology

2. Institution & address:

Harvard Medical School
25 Shattuck Street
Boston, Massachusetts 02115

3. Department(s) where research will be done or collaboration provided:

Department of Physiology, Harvard Medical School
Psychobiology Laboratory, Department of Psychiatry, Harvard Medical School
Department of Nutrition, Harvard School of Public Health

4. Short title of study:

Behavioral Hypertension and Arteriosclerosis: Effects of Nicotine and Carbon Monoxide

5. Proposed renewal date:

January 1, 1974.

6. How results to date have changed earlier specific research aims:

No change in specific Research Aims.
Specific aims of this research program are to determine the effects of nicotine and carbon monoxide on behavioral performances, heart rate, arterial blood pressure, serum cholesterol, and atherosclerosis in the squirrel monkey.

7. How results to date have changed earlier working hypothesis:

No change in Working Hypothesis

(a) Nicotine administered in small amounts over long periods of time suppresses cardiovascular responses to certain behavioral procedures, and

(b) Carbon monoxide administered in low concentrations over long periods of time has inconsequential effects on long term hypertensive and arteriosclerotic response to certain behavioral procedures and atherogenic diets.

8. Any additional facilities now required? Describe briefly:

None.

9. Any changes in personnel? Append biographical sketches of new key professional personnel:

None.

10. Append outline of experimental protocol for ensuing year. Appendix II.

11. List publications or papers in press resulting from this or closely related work. (append reprints or manuscripts not previously sent).

None.

12. Summary progress report (append in standard form as separate document, unless recently submitted). Appendix III.

13. Budget for the coming year: see Appendix IV.

A. Salaries (give names or state "to be recruited")

Professional (give % time of investigator(s) even if no salary requested)	% time	Amount (including fringe benefits)
A.C. Barger	15	None
P.B. Dews	15	None
J.A. Herd	25	None
R.T. Kelleher	25	None
W.H. Morse	25	None
Technical		
W. Goulding, Research Assistant I	100	9,094
S.A. Grose, Research Associate	100	14,623
L. King, Research Assistant II	100	12,310

Sub-Total for A 36,027

B. Consumable supplies (by major categories)

Animal purchase, care, food and supplies	3,451
Pathology	500
Electrical supplies	1,000
Physiological supplies	1,000
Surgical supplies	500

Sub-Total for B 6,451

C. Other expenses (itemize)

Art work, photography and publication costs

Sub-Total for C 1,000

Running Total of A + B + C 43,478

D. Permanent equipment (itemize)

None

Sub-Total for D - -

E. Indirect costs (15% of A+B+C) E 6,522

Total request $50,000.00

14. Other sources of financial support:

List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Specialized Center for Research in Hypertension (SCOR)	USPHS HL 14150	$1,534,351.	6.1.71-5.31.76
Kidney Function in Experimental Heart Failure	USPHS HL 02493	149,000.	9.1.69-8.31.74
Basic Types of Effects of Drugs on Behavior	USPHS MH 02094	105,141.	12.1.70-11.30.75
Central Control of Distribution of Organ Blood Flow	USPHS HL 09154	45,148.	9.1.72-8.31.75
Effects of Drugs on Reactions to Aversive Stimuli	USPHS MH 07658	219,126.	5.1.70-4.30.75
Biotechnology Resource in Electronprobe Microanalysis	USPHS 1 P07-RR00679 1 R01-HL15552	804,069.	6.26.72-8.31.77

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
None			

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It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Principal investigator

Typed Name A. Clifford Barger

Signature A. Clifford Barger Date 7/24/73

Telephone 617 734-3300 486
Area Code Number Extension

Checks payable to

President and Fellows of Harvard College

Mailing address for check:

25 Shattuck Street

Boston, Massachusetts 02115

Responsible officer of institution

Typed Name Henry C. Meadow

Title Executive Secretary, Committee on Research & Development

Signature Henry C. Meadow Date 7/24/73

Telephone 617 734-3300 441
Area Code Number Extension

Appendix I.

1. Names of investigators including titles and degrees:

A. C. Barger, M.D. Robert Henry Pfeiffer Professor of Physiology

P. B. Dews, M.B., Ch.B., Ph.D. Stanley Cobb Professor of Psychiatry and Psychobiology

K. C. Hayes, D.V.M., Ph.D. Assistant Professor of Nutrition in the School of Public Health

J. A. Herd, M.D. Associate Professor of Physiology

R. T. Kelleher, Ph.D. Professor of Psychobiology in the Department of Psychiatry

W. H. Morse, Ph.D. Associate Professor of Psychobiology in the Department of Psychiatry

R. Beeuwkes, III, Ph.D. Assistant Professor of Physiology

L. D. Byrd, Ph.D. Instructor in Psychobiology in the Department of Psychiatry.

S. R. Goldberg, Ph.D. Research Fellow in Psychobiology in the Department of Psychiatry.

N. P. Westmoreland, D.V.M., Ph.D. Assistant Professor of Nutrition in the School of Public Health

S. A. Grose, B.S. Research Associate in Psychobiology in the Department of Physiology

N. R. Leclair, M.S.E. Electronic Engineer

Appendix II.

Item 10. Outline of Experimental Protocols for Ensuing Year.

1. Arterial blood pressure and heart rate in the squirrel monkey during behavioral procedures following the administration of nicotine.

Blood pressures and heart rates of squirrel monkeys will be measured using an oscillometric technique before and after daily sessions under operant conditioning procedures. As soon as consistent behavioral and cardiovascular responses to the operant conditioning schedules have been established, nicotine tartrate (0.01 to 1.0 mg/kg, i.m.), chlordiazepoxide (1.0 to 30.0 mg/kg, i.m.), d-amphetamine (0.01 to 1.0 mg/kg, i.m.) or saline (1.0 ml, i.m.) will be administered before the start of each daily session. Additional experiments will also be performed in which these agents are administered chronically over long periods of time.

2. Effects of nicotine on hypercholesterolemia and aortic atherosclerosis in the squirrel monkey during administration of an atherogenic diet.

Young adult squirrel monkeys will be trained initially to eat a semi-purified diet of normal composition and, later, a diet containing moderate amounts of saturated fats (8 g %) and cholesterol (0.1 to 0.2 g %). Venous blood will be drawn repeatedly for measurements of serum cholesterol levels. As soon as intake of food and water, body weight, and serum cholesterol values of all subjects have stabilized during the administration of an atherogenic diet, nicotine tartrate (0.01 to 1.0 mg/kg·day, p.o.) will be administered chronically. Some animals will be continued on each regimen for 16 weeks and then examined using standard techniques for investigating gross and microscopic vascular pathologic anatomy. Some animals will be treated with propranolol (0.1 to 10 mg/kg·day, p.o.) or guanethidine (0.01 to 1.0 mg/kg·day, p.o.) in addition to cholesterol and saturated fats in the diet and nicotine tartrate in the drinking water .

3. Arterial blood pressure and oxygen consumption in the squirrel monkey at high and low ambient temperatures.

Blood pressures, heart rates, and oxygen consumptions of adult squirrel monkeys will be measured before and after daily sessions under operant conditioning procedures at high and low ambient temperatures. As soon as consistent behavioral, metabolic, and cardiovascular responses have been established, nicotine tartrate (0.01 to 1.0 mg/kg, i.m.) or saline (1.0 ml, i.m.) will be administered before the start of each daily session. Some animals will be subjected to surgical denervation of the carotid sinuses and the aortic arch to enhance the cardiovascular and metabolic responses to behavioral procedures at low ambient temperatures. The role of the sympathetic nervous system in mediating the responses to behavioral procedures at low ambient temperatures will be studied using intravenous infusions of alpha-adrenergic agonists such as phenylephrine and vasodilator substances such as glyceryltrinitrate, diazoxide, and phentolamine.

4. Effects of carbon monoxide on hypercholesterolemia and aortic atherosclerosis in the squirrel monkey during administration of an atherogenic diet.

In these studies, an experimental protocol similar to that described in section 2, Item 10 above will be followed. As soon as intakes of food and water, body weights, and serum cholesterol values have stabilized during the administration of an atherogenic diet, carbon monoxide will be added to the inspired air in concentrations of 50 to 250 p.p.m. Effects of carbon monoxide

will be assessed initially by periodic measurements of serum cholesterol values. Results from initial experiments will later be used to determine the amounts of cholesterol, saturated fats, and concentrations of carbon monoxide that should be tested systematically for their effects on aortic atherosclerosis in the squirrel monkey.